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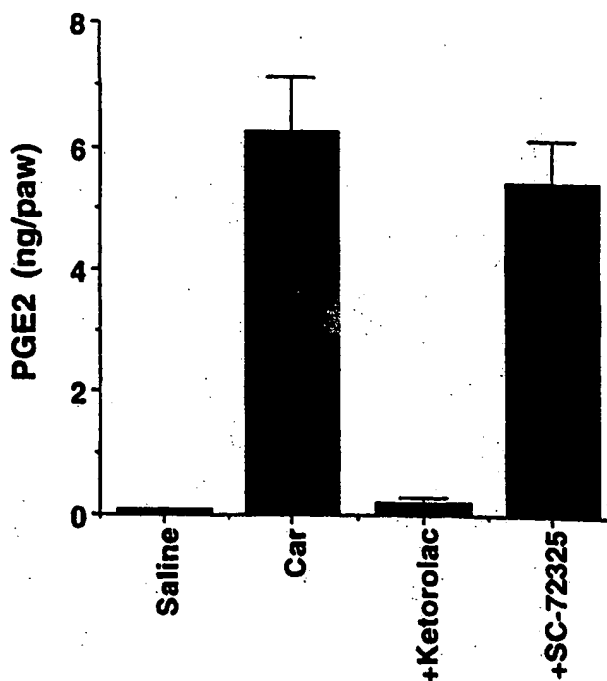
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(21) International Application Number: <b>PCT/US98/12231</b> (22) International Filing Date: <b>15 June 1998 (15.06.98)</b> (30) Priority Data: 60/050,402                      20 June 1997 (20.06.97) <b>US</b> (71) Applicant (for all designated States except US): <b>G.D. SEARLE &amp; CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).</b> (72) Inventor; and (75) Inventor/Applicant (for US only): <b>SALVEMINI, Daniela [IT/US]; 1820 Orchard Hill Drive, Creve Coeur, MO 63017 (US).</b> (74) Agents: <b>ROTH, Michael, J. et al.; G.D. Searle &amp; Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).</b>		(81) Designated States: <b>AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</b>  <b>Published</b> <i>With international search report.          Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	

(54) Title: ANALGESIC METHODS USING SYNTHETIC CATALYSTS FOR THE DISMUTATION OF SUPEROXIDE RADICALS

(57) Abstract

Synthetic low molecular weight catalysts for the dismutation of superoxide are potent analgesics that are effective in elevating the pain threshold in hyperalgesic conditions such as arthritis, and also operate to prevent or reverse tolerance to opioid analgesics.



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## ANALGESIC METHODS USING SYNTHETIC CATALYSTS FOR THE DISMUTATION OF SUPEROXIDE RADICALS

### Technical Field

5           This invention relates to the treatment of humans and lower animals in pain management: to prevent or relieve pain, to prevent or reverse tolerance to opioid analgesics and hyperalgesia associated with prolonged opioid treatment, and to prevent or reduce symptoms of opioid withdrawal and related withdrawal syndromes.

### Background Art

10           Numerous analgesics are known to medical science. Many analgesics fall into one of two large categories -- nonsteroidal analgesic/anti-inflammatory drugs (NSAIDs) and opioids. NSAIDs operate by inhibiting cyclooxygenase enzymes and thereby the synthesis of prostaglandins. Prostaglandins sensitize pain receptors, lowering the pain threshold and making normal stimuli, such as touch and stretch sensations, painful.

15           NSAIDs can be quite effective at returning the lowered pain threshold to normal but do not elevate the pain threshold.

          A second class of pain relievers, opioids or opioids, operate by mimicking natural peptides such as enkephalins and endorphins to stimulate one or more of the  $\mu$ -,  $\delta$ - and  $\kappa$ -receptor systems in the nervous system. Opioids elevate the pain threshold so that

20           normally painful stimuli are perceived as less painful or even euphoric. Opioids are commonly used in the clinical management of severe pain, including chronic severe pain of the kind experienced by cancer patients.

          Capsaicin and its derivatives operate by depleting local stores of substance P, a neuropeptide involved in the transmission of pain impulses and are used in several OTC

25           analgesic products.

          Each of these classes of compounds has inherent problems and limitations. The opioid analgesics are antagonized by analogous N-allyl compounds such as naloxone; the NSAID analgesics are not. NSAIDs that are nonselective for the cyclooxygenase 2 produced in inflammation (COX-2) also inhibit constitutive cyclooxygenase 1 (COX-1),

causing undesirable damage to the gastric mucosa. They have limited effectiveness as analgesics in lowering an elevated threshold to normal and are generally used for mild to moderate pain. They are also ineffective drugs for elevation of the pain threshold above normal levels, which prevents their use in pain such as surgical pain where an underlying  
5 pathological condition has not elevated the pain threshold.

Opioids have problems with tolerance and dependency, so that over a course of therapy increasing dosages of compound are required to achieve the same level of analgesia, and cessation of opioid administration when analgesia is no longer needed elicits a withdrawal syndrome with unpleasant and potentially serious symptoms. The  
10 dependency and withdrawal syndrome both make it difficult for the clinician to discontinue opioid therapy even when the opioids are no longer effective in relieving pain because of the development of tolerance. Narcotic induced hyperalgesia (NIH) can also develop in association with tolerance to the opioids. All of these factors limit the usefulness of opioids in the management of chronic severe pain, despite their potency.

No adequate strategy has been devised to overcome the development of opioid tolerance and provide an ongoing approach to the management of chronic severe pain. Mechanisms of tolerance are not well understood but are known to involve the NMDA receptor, since the NMDA receptor antagonist MK-801 has been shown in rats to prevent morphine tolerance. NMDA stimulates nitric oxide synthase (NOS) and NOS has been  
20 observed histochemically in tissues that contain opioid receptors and are important in the pain response, such as the amygdala, cortical gray matter, and the *substantia gelatinosa* of the spinal cord. Non-selective NOS inhibitors such as NG-nitroarginine prevent and reverse morphine tolerance. However, nonselective inhibition of NOS is associated with a vast array of undesirable side effects, including hypertension, increased platelet and  
25 white blood cell reactivity, decreased cerebral blood flow, and gastrointestinal and renal toxicity.

Capsaicin and some of its derivatives, in addition to producing analgesia, also elicit a burning sensation. This effect is responsible for the pungency of hot peppers

(*Capsicum* spp.) and limits the applicability of many members of this series of compounds.

For these and other reasons, a continuing need exists for new high potency analgesics. A need also exists for methods for reversing tolerance to opioid analgesics so that patients who require these drugs for pain over extended periods can do so without loss of potency and efficacy.

One object of this invention is to provide new methods for the prevention and relief of mild to severe pain by identifying a new biological activity of a class of synthetic catalyst compounds, and by specifying a new indication for those compounds.

It is another object of this invention to provide methods for preventing and reversing tolerance to opioid analgesics by identifying another new biological activity of that class of catalysts and another new indication for those compounds.

These and other objects of the invention will be evident from the following disclosure.

#### **Brief Description of the Drawings**

Figure 1 is a graph depicting the results of a study on the inhibition of carrageenan-induced hyperalgesia by intravenously injected SC-72325. The drug was given at 3 hours post carrageenan injection.

Figures 2 and 3 are graphs depicting the results of a study on inhibition of carrageenan-induced hyperalgesia by intramuscular injection of either SOD mimic compound SC-72325 (Example 157) or the nonsteroidal anti-inflammatory drug ketorolac.

Figure 4 is a graph depicting the results of a study comparing the effects of SC-72325 versus ketorolac on carrageenan-induced increase of PGE-2 in cerebrospinal fluid.

Figure 5 is a graph depicting the results of a study comparing the effects of SC-72325 versus ketorolac on carrageenan-induced release of PGE-2 in paw exudate.

#### **Disclosure of the Invention**

This invention is based upon surprising discoveries involving certain organometallic complexes designed as synthetic catalysts for use in the body. These

catalysts have been designed as synthetic replacements for or adjuncts to the naturally occurring enzyme superoxide dismutase (SOD).

Naturally occurring SOD scavenges and eliminates the toxicity of free superoxide radicals ( $O_2^{\cdot -}$ ) liberated by certain metabolic reactions. Although these free radicals play a major (and deleterious) role in the inflammatory response and other toxic reactions to injury, neither superoxide nor SOD has been known to be directly involved in pain perception. In addition, SOD has a very short biological half-life, on the order of seconds or minutes rather than hours, so it would be considered unsuitable for treatment of conditions in which increased dismutation of superoxide radicals would be desirable over periods of from minutes to days.

Dismutation of superoxide radicals is catalyzed by a coordinated transition metal ion. In the natural SOD enzyme, the metal is manganese, copper or zinc and the coordination complex is a conventional protein structure. Synthetic SOD catalysts also use transition metals, complexed with low molecular weight organic ligands, generally polydentate N-containing macrocycles. These molecules have been designed to be highly efficient and to overcome the pharmacokinetic disadvantages of natural SOD enzyme. The  $k_{cat}$  of some of these compounds is as high as about  $10^9$  (see Example 165), indicating extraordinary catalytic efficiency, as effective as the natural enzyme and approaching the theoretical rate at which diffusion can deliver free radical substrate to the catalyst under biological conditions. They also have oil:water partition coefficients ( $_{log}P$ ) that provide excellent bioavailability, and stability in the body on the order of hours to days. Their small size and low molecular weight makes it possible for the synthetic catalysts to cross membrane barriers that restrict movement of natural SOD, and their non-protein structure reduces the risk of allergic reactions that have been a problem with the administration of protein-based recombinant SOD. Finally, natural SOD produces hydrogen peroxide in the process of dismutating superoxide, yet hydrogen peroxide inhibits natural SOD, effectively self-limiting the efficacy of the natural compound. In contrast, synthetic small-molecule SOD catalysts are not susceptible to the action of hydrogen peroxide and thus retain their effectiveness.

Synthetic SOD catalysts have been proposed in the past for the treatment and prevention of inflammation, ischemia-reperfusion injury, and similar conditions where tissue damage is mediated by levels of free superoxide radicals that overwhelm natural SOD, but they have not been proposed for use as analgesics in the treatment of pain.

5        It has now been discovered that synthetic SOD catalysts are highly effective as analgesics to prevent or provide relief from pain in conditions in which the pain threshold is elevated. It has also been discovered that these same compounds are effective in preventing or reversing tolerance to opioid analgesics, that are used to elevate the pain threshold above normal levels.

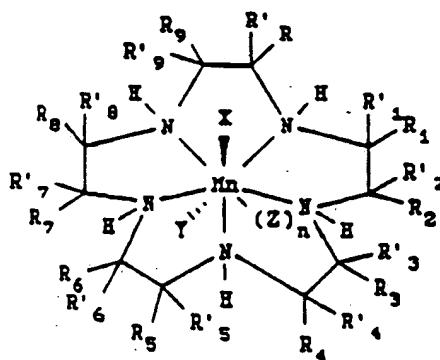
10        No known mechanism accounts for the analgesic properties of these compounds. However, the data shown in the examples illustrate that these compounds can be as effective as morphine in preventing and relieving certain kinds of pain. Y. Lin et al., *Int. J. Maxillofac. Surg.* 23:428-429 (1994) reported the use of intra-articular injections of human Cu/Zn superoxide dismutase as a nonsteroidal anti-inflammatory in the treatment  
15 of temporomandibular joint dysfunction. Positive response in terms of mandibular movement and pain was observed in 83% of patients. The authors note that the results "are remarkable because SOD has been studied and shown to exert no peripheral or central analgesic effect." They attribute the reduction in pain to the reduction in tissue injury and inflammation associated with TMJ dysfunction.

20        Similarly, no known mechanism accounts for the ability of these compounds to prevent or reverse tolerance to opioids. G.I. Elmer et al., *Euro. J. Pharmacol.* 283 (1995) 227-232, reported that transgenic mice expressing the human Cu/Zn superoxide dismutase gene had an increase in  $\mu$ -opioid receptor concentration in dopaminergic related tissues and the central grey area of the CNS, which was associated with a dose-  
25 related increased sensitivity to  $\mu$ -receptor agonists such as morphine. At the same time the authors also observed conflicting effects of transgenic SOD on  $\delta$ -receptor agonists (mice heterozygous for the transgene were more sensitive than homozygotes, which were more sensitive than untransformed mice) and observed no effect of transgenic SOD on  $\kappa$ -receptor agonists.

Superoxide dismutase activity is known to play a critical role in regulating the redox state of the cell, as reported by J.L. Cadet, *Int. J. Neurosci.* **40**, 13 (1988). This in turn is reported by Marzullo and Hine, *Science* **208**, 1171 (1980) to significantly affect *in vitro*  $\mu$ - and  $\delta$ -opioid binding.

#### 5 Modes for Carrying Out the Invention

In particular, this invention provides a method of producing analgesia in a human or lower mammal patient, comprising administering to the patient an analgesic amount of a functional synthetic catalyst for the dismutation of superoxide radicals. Based on the data obtained, it is reasonable to expect that any superoxide dismutase catalyst will be effective in the practice of this invention. A preferred synthetic catalyst is a coordination complex of transition metal with an organic ligand. Preferred transition metals are copper, manganese and zinc. Manganese is most preferred. In general, the organic ligand is a N-containing macrocycle, and most preferred ligands are selected from the group consisting of compounds of the formula



25 wherein R, R', R<sub>1</sub>, R'<sub>1</sub>, R<sub>2</sub>, R'<sub>2</sub>, R<sub>3</sub>, R'<sub>3</sub>, R<sub>4</sub>, R'<sub>4</sub>, R<sub>5</sub>, R'<sub>5</sub>, R<sub>6</sub>, R'<sub>6</sub>, R<sub>7</sub>, R'<sub>7</sub>, R<sub>8</sub>, R'<sub>8</sub>, R<sub>9</sub>, and R'<sub>9</sub>, independently are selected from the group consisting of hydrogen and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylcycloalkyl, alkylcycloalkyl, cycloalkenylalkyl, alkenylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkenyl, heterocyclic, aryl and aralkyl radicals, or R or R' and R<sub>1</sub> or R'<sub>1</sub>, R<sub>2</sub> or R'<sub>2</sub> and R<sub>3</sub> or R'<sub>3</sub>,  
 30 R<sub>4</sub> or R'<sub>4</sub> and R<sub>5</sub> or R'<sub>5</sub>, R<sub>6</sub> or R'<sub>6</sub> and R<sub>7</sub> or R'<sub>7</sub>, and R<sub>8</sub> or R'<sub>8</sub> and R<sub>9</sub> or R'<sub>9</sub>, together with



- the carbon atoms to which they are attached independently form a saturated, partially saturated or unsaturated cyclic ring structure having 3 to 20 carbon atoms; or R or R', R<sub>1</sub> or R'<sub>1</sub>, and R<sub>2</sub> or R'<sub>2</sub>, R<sub>3</sub> or R'<sub>3</sub>, and R<sub>4</sub> or R'<sub>4</sub>, R<sub>5</sub> or R'<sub>5</sub>, and R<sub>6</sub> or R'<sub>6</sub>, R<sub>7</sub> or R'<sub>7</sub>, and R<sub>8</sub> or R'<sub>8</sub>, and R<sub>9</sub> or R'<sub>9</sub>, together with the carbon atoms to which they are attached
- 5 independently form a nitrogen-containing heterocycle having 2 to 20 carbon atoms provided that when the nitrogen containing heterocycle is an aromatic heterocycle that does not have a hydrogen attached to the nitrogen, the hydrogen attached to the nitrogen in the macrocycle and the R groups attached to the same carbon atoms of the macrocycle are absent; R and R', R<sub>1</sub> and R'<sub>1</sub>, R<sub>2</sub> and R'<sub>2</sub>, R<sub>3</sub> and R'<sub>3</sub>, R<sub>4</sub> and R'<sub>4</sub>, R<sub>5</sub> and R'<sub>5</sub>, R<sub>6</sub> and R'<sub>6</sub>, R<sub>7</sub> and R'<sub>7</sub>, R<sub>8</sub> and R'<sub>8</sub> and R<sub>9</sub> and R'<sub>9</sub>, together with the carbon atom to which they
- 10 are attached independently form a saturated, partially saturated or unsaturated ring structure having 3 to 20 carbon atoms; or two of R, R', R<sub>1</sub>, R'<sub>1</sub>, R<sub>2</sub>, R'<sub>2</sub>, R<sub>3</sub>, R'<sub>3</sub>, R<sub>4</sub>, R'<sub>4</sub>, R<sub>5</sub>, R'<sub>5</sub>, R<sub>6</sub>, R'<sub>6</sub>, R<sub>7</sub>, R'<sub>7</sub>, R<sub>8</sub>, R'<sub>8</sub>, R<sub>9</sub>, and R'<sub>9</sub>, attached to different carbon atoms of the macrocycle are bound to form a strap structure of the formula
- 15  $-(CH_2)_x-M-(CH_2)_w-L-(CH_2)_z-J-(CH_2)_y-$  wherein w, x, y and z independently are integers from 0 to 10 and M, L and J are independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, alkaryl, alkheteroaryl, aza, amido, ammonium, thio, sulfonyl, sulfinyl, sulfonamido, phosphonyl, phosphinyl, phosphino, phosphonium, keto, ester, carbamyl, ureido, thiocarbonyl, borate, borane, boraza, silyl, siloxy and silaza radicals, and combinations thereof; wherein X, Y
- 20 and Z are pharmaceutically acceptable counterions or together are a pharmaceutically acceptable polydentate ligand, or are independently attached to one or more of the R groups and n is an integer from 0 to 3.

By an "analgesic amount" of the synthetic SOD catalysts herein is meant an

25 amount that significantly prevents or alleviates pain in the human or lower animal being treated. At a certain level stimuli are perceived as painful, while below that level they are not. This level is referred to as the pain threshold. Healthy, normal subjects exhibit a normal pain threshold that can be quantified for a given stimulus. A normal healthy individual perceives a pin prick as painful, but does not perceive the movement of a joint

within its normal range of motion as painful. An individual suffering from arthritis has a lowered pain threshold and will perceive such normal movement as painful. An individual suffering from sunburn has a lowered pain threshold and may perceive the touch of a finger to be as painful as a normal individual perceives a pin prick. Because  
5 these compounds operate to elevate a lowered pain threshold, they will be effective in the treatment of such pain, and an "analgesic amount" of synthetic SOD catalysts in the treatment methods provided here also means an amount that significantly elevates the pain threshold above its pre-treatment level or prevents the pain threshold from being lowered by a pathological condition. From the standpoint of the pharmacologist and  
10 pharmaceutical scientist, this can be measured prospectively using common animal models such as the phenylquinone writhing model, the rat tail flick (radiant heat) model, the carrageenan inflammation model, the Freund's adjuvant model, and other pain models well known to pharmacological science. From the standpoint of the clinician, this can be measured according to the subjective response of each patient to a unit dose of the  
15 compound, and subsequent doses can be titrated to achieve the desired level of analgesia within the therapeutic range of the compound employed.

By an "amount sufficient to prevent or reverse tolerance to opioids" is meant The dual administration of a superoxide dismutase catalyst together with an opioid such as morphine or fentanyl allows lower doses of the morphine or fentanyl to elicit its  
20 analgesic effects while limiting its side effects. Moreover, a superoxide dismutase catalyst can reverse opioid tolerance in patients who have already developed tolerance. Thus, the superoxide dismutase catalysts restore the analgesic effect lost during prolonged treatment with an opioid. These catalysts prevent or reverse the tolerance to opioids without many of the side effects of other compounds proposed for this purpose,  
25 such as clonidine and buprenorphine. And in contrast to other proposed compounds, such as inhibitors of inducible nitric oxide synthase, the superoxide dismutase catalysts themselves have potent analgesic effects that are useful in hyperalgesic conditions such as burns, arthritis and other inflammatory diseases, migraine, and pain associated with tumor infiltration and cancer therapy.

The compounds of this invention are also useful as adjuncts in the prevention and treatment of pain with opioid analgesics, nitric oxide donors or nonsteroidal anti-inflammatory compounds. In preferred embodiments, the superoxide dismutase catalyst is administered conjointly with the opioid, NO<sub>2</sub> donor or NSAID compound.

5 Administered in conjunction with an opioid, the superoxide dismutase catalyst potentiates the opioid and prevents development of tolerance and hyperalgesia. Administered after opioid tolerance, hyperalgesia and/or dependency have developed, the superoxide dismutase catalyst reverses the tolerance and hyperalgesia and reduces the symptoms of the withdrawal syndrome. Administered in conjunction with an NSAID compound or  
10 nitric oxide donor, the superoxide dismutase catalyst potentiates both the analgesia and the inflammatory action of the NSAID or NO<sub>2</sub> donor. These drug moieties can also be linked to provide bifunctional compounds of the formula A<sub>n</sub>-Q<sub>m</sub>, wherein A is a superoxide dismutase catalyst moiety, Q is selected from nonsteroidal anti-inflammatory drug moieties, nitric oxide donor moieties and opioid analgesic drug moieties, and n and  
15 m are independently integers from 1 to 3. Depending upon the selection of A and Q, this can easily be done by substituting the NSAID or opioid moiety for one or more of counterion/ligands X, Y and Z in the preferred formula above. A simple approach to providing a combination containing a nitric oxide donor is to attach one or more nitrate or nitrite groups to the superoxide dismutase compound.

20 While not intending to be limited by theory, it is believed that the opioid withdrawal syndrome has many symptoms in common with the withdrawal syndromes associated with other addictive compounds and behaviors, including symptoms of withdrawal from cocaine, nicotine, and eating disorders such as anorexia and bulimia, especially the hyperreflexia and hyperalgesia associated with withdrawal. Accordingly,  
25 this invention also provides a method of preventing and treating symptoms of addiction withdrawal, by administering to a patient in need of such treatment an amount of a superoxide dismutase catalyst that is safe and effective to prevent or reduce such symptoms.

A safe and effective amount of the compounds used in the practice of this invention is an amount that provides analgesia, thereby alleviating or preventing the pain being treated, at a reasonable benefit/risk ratio as is intended with any medical treatment. In using the compounds for the reversal of opioid tolerance or reduction of withdrawal symptoms, these endpoints are used rather than analgesia. Obviously, the amount of catalyst used will vary with such factors as the particular condition that is being treated, the severity of the condition, the duration of the treatment, the physical condition of the patient, the nature of concurrent therapy (if any), the route of administration, the specific formulation and carrier employed, and the solubility and concentration of catalyst therein.

By "systemic administration" is meant the introduction of the catalyst or composition containing the catalyst into the tissues of the body, other than by topical application. Systemic administration thus includes, without limitation, oral and parenteral administration.

Depending upon the particular route of administration, and compatibility with the active compound chosen, a variety of pharmaceutically-acceptable carriers, well-known in the art, may be used. These include solid or liquid filler, diluents, hydrotropes, excipients, surface-active agents, and encapsulating substances. The amount of the carrier employed in conjunction with the catalyst is sufficient to provide a practical quantity of material per unit dose.

Pharmaceutically-acceptable carriers for systemic administration that may be incorporated into the compositions of this invention, include sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable oil, synthetic oils, polyols, alginic acid, phosphate buffer solutions, emulsifiers, isotonic saline, and pyrogen-free water.

The catalysts can be administered parenterally in combination with a pharmaceutically acceptable carrier such as corn oil, Cremophor EL or sterile, pyrogen-free water and a water-miscible solvent (e.g., ethyl alcohol) at a practical amount of the catalyst per dose. Preferably, the pharmaceutically- acceptable carrier, in compositions for parenteral administration, comprises at least about 90% by weight of the total

composition. Parenteral administration can be by subcutaneous, intradermal, intramuscular, intrathecal, intraarticular or intravenous injection. The dosage by these modes of administration is usually in the range of from about 0.1 mg. to about 20 mg per day.

- 5           Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. These oral forms comprise a safe and effective amount, usually at least about 5%, and preferably from about 25% to about 50% of the catalyst. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated or multiple compressed, containing suitable binders, lubricants, diluents,
- 10   disintegrating agents, coloring agents, flavoring agents, preservatives, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from noneffervescent granules and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents,
- 15   diluents, sweeteners, melting agents, coloring agents, and flavoring agents. Preferred carriers for oral administration include gelatin, propylene glycol, ethyl oleate, cottonseed oil and sesame oil. Specific examples of pharmaceutically-acceptable carriers and excipients that may be used to formulate oral dosage forms containing the catalysts used in this invention, are described in U.S. Pat.No. 3,903,297, Robert, issued Sept. 2, 1975,
- 20   incorporated by reference herein. Techniques and compositions for making solid oral dosage forms are described in Marshall, "Solid Oral Dosage Forms," Modern Pharmaceutics, Vol. 7 (Banker and Rhodes, editors), 359-427 (1979), incorporated by reference herein.

- By "pharmaceutically acceptable salts" is meant those salts that are safe for
- 25   topical or systemic administration. These salts include the sodium, potassium, calcium, magnesium, and ammonium salts.

#### **Carrageenan paw hyperalgesia testing**

Sprague-Dawley rats (175-200 g, Harlan Sprague Dawley, Indianapolis, Indiana, USA) were housed and cared for under the guidelines of the Institutional Animal Care

and Use Committee. They received a subplantar injection of carrageenan (0.1 mL of a 1% suspension in 0.85% saline) into the right hind paw. At three hours post-carrageenan, when hyperalgesia is normally at a maximum, the test compound was administered intravenously at dosages of from 1-6 mg./kg. Hyperalgesia is assessed at thirty minutes to three hours post-administration of test compound.

#### Example 1

SOD catalyst compounds were evaluated in the carrageenan hyperalgesia model described above. Results were as follows:

	<u>Compound</u>	<u>Result</u>
10	SC-71354	No effect at tested dosages by intravenous injection*
	SC-69604	No effect at tested dosages by intravenous injection
	SC-71449	No effect at tested dosages by intravenous injection
	SC-72325	Inhibited hyperalgesia 64% at 30 minutes
	SC-73770	Inhibited hyperalgesia 72% at 30 minutes

15 \* Higher dosage levels and other routes of administration were not tested for any of the compounds.

#### Example 2

Analgesia provided by intravenous SC-72325 was evaluated over time in the carrageenan model. Results are shown in Figure 1.

#### 20 Example 3

Analgesia provided by intramuscular injection of SC-72325 was evaluated over time in the carrageenan model in comparison to the anti-inflammatory drug ketorolac. Results are shown in Figures 2 and 3, respectively.

#### Example 4

25 To determine whether the SOD catalyst compounds provide analgesia by some action on the prostaglandin-leukotriene system, release of prostaglandin PGE<sub>2</sub> was measured in rat paw exudate from the carrageenan model as well as in spinal cord fluid. Saline was used as a non-inflamed control and the anti-inflammatory ketorolac was used as a positive anti-inflammatory control. Results are shown in Figures 4 and 5. SC-72325

did not significantly reduce release of PGE2 compared to the carrageenan-injected but untreated rats. Ketorolac treated rats had levels of PGE2 release similar to non-carrageenan injected animals.

#### Example 5

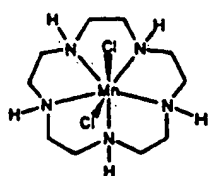
5           Mice were treated twice a day with either saline (naïve) or morphine (s.c., 10 mg/kg) for a period of 4 days to induce tolerance. For comparison, a dose of 10 mg, or less than 0.15 mg/kg every 4 to 10 hours, is a morphine dosage routinely prescribed for the 70 kg. human adult with severe pain. On day 5, all mice received a subcutaneous challenge dose of 3 mg./kg morphine and the level of analgesia was measured 30 minutes  
10 later. Results are shown graphically in Figure 6. Dose response measurements in normal mice have indicated that a challenge dose of 3 mg./ kg. would elicit 90% analgesia in naïve or non-tolerant mice when assessed by the standard hot plate test. In this example, mice that were treated with morphine for 4 days showed a decreased analgesic effect from morphine on day 5 when compared with the naïve mice. Tolerance to morphine was  
15 eliminated in mice that were treated with the superoxide dismutase catalyst SC-72325 administered intraperitoneally.

#### Examples 6-167

          The following compounds were made for use as superoxide dismutase catalysts or as ligands for combination with transition metal ions for use as superoxide dismutase  
20 catalysts within the scope of the invention. The catalytic rate constant  $k_{cat}$  is given for each compound. For  $k_{cat}$  values marked with an asterisk, the  $k_{cat}$  was measured at a pH of 8.1. For all other compounds the  $k_{cat}$  was measured at pH 7.4. Compounds marked NT were made but not tested. The ligands of Examples 11, 101, 123-135 and 138-148 were not expected to have activity without the metal ion and most were not tested. However,  
25 as can be seen by comparison of Examples 148 and 149, insertion of the metal ion into the ligand forms a complex with good superoxide dismutase activity.

Example 6

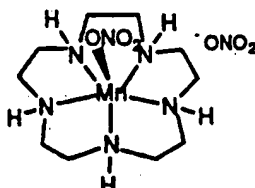
Example 7



SC-52608

 $4.13 \times 10^7$ 

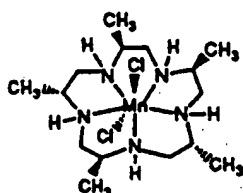
Example 8



SC-53520

 $2.30 \times 10^{17}$ 

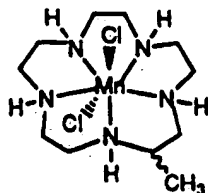
Example 9



SC-55509

 $2.60 \times 10^{17}$ 

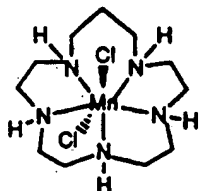
Example 10



SC-52609

 $2.60 \times 10^{17}$ 

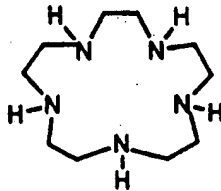
Example 11



SC-52610

 $0.110 \times 10^7$ 

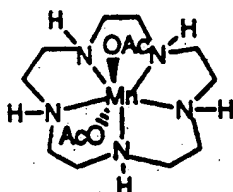
Example 12



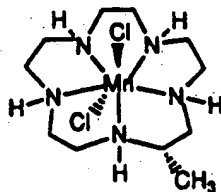
SC-52612

0.00

Example 13



SC-52613

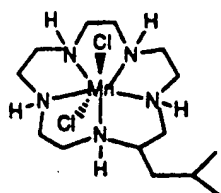
 $1.85 \times 10^{17}$ 

SC-52633

 $2.39 \times 10^{17}$



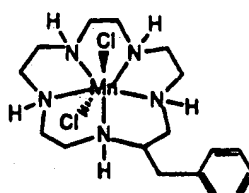
Example 14



SC-52718

 $1.91 \times 10^{7^*}$ 

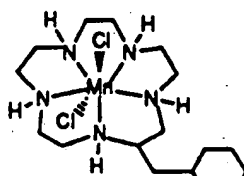
Example 15



SC-52965

 $7.21 \times 10^7$ 

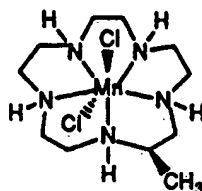
Example 16



SC-53519

 $2.07 \times 10^{7^*}$ 

Example 17

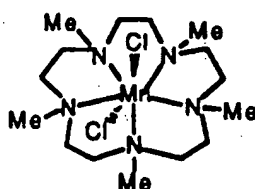


SC-53565

 $6.65 \times 10^7$ 

5

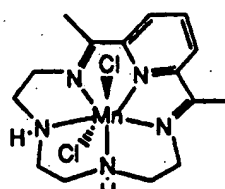
Example 18



SC-54383

0

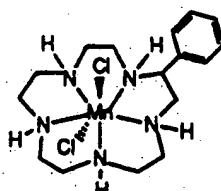
Example 19



SC-54385

0

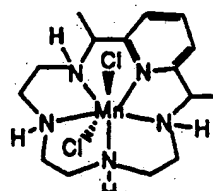
Example 20



SC-54415

 $1.76 \times 10^{7^*}$ 

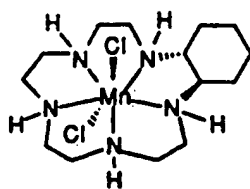
Example 21



SC-54416

 $1.00 \times 10^{7^*}$

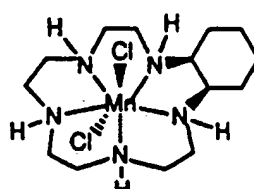
Example 22



SC-54417

 $9.09 \times 10^7$ 

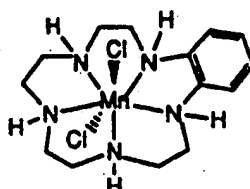
Example 23



SC-54653

 $1.86 \times 10^{10}$ 

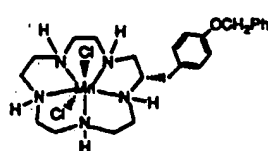
Example 24



SC-54739

 $4.09 \times 10^7$ 

Example 25

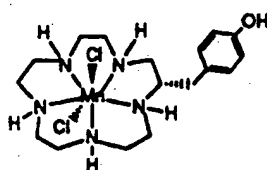


SC-54917

 $1.70 \times 10^{10}$ 

5

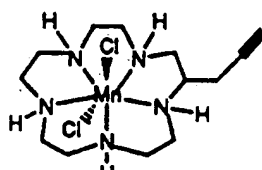
Example 26



SC-55118

 $1.82 \times 10^{10}$ 

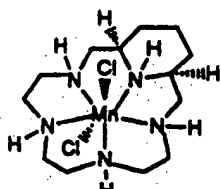
Example 27



SC-55182

 $1.75 \times 10^{10}$ 

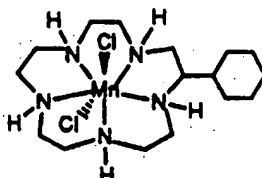
Example 28



SC-55183

 $0.680 \times 10^{10}$ 

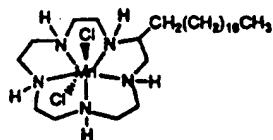
Example 29



SC-55184

 $1.42 \times 10^{10}$

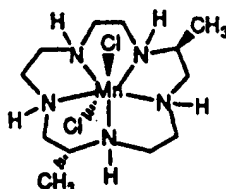
Example 30



SC-55185

 $1.91 \times 10^{7^*}$ 

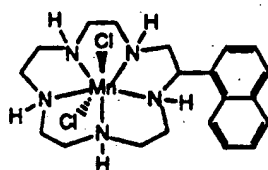
Example 31



SC-55186

 $1.64 \times 10^{7^*}$ 

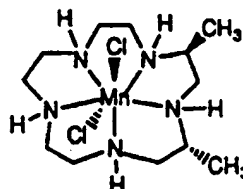
Example 32



SC-55187

 $0.700 \times 10^{7^*}$ 

Example 33

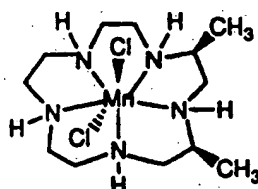


SC-55333

 $6.70 \times 10^{7^*}$ 

5

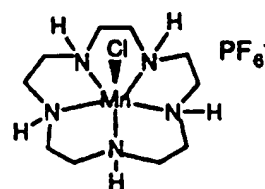
Example 34



SC-55334

 $2.36 \times 10^{7^*}$ 

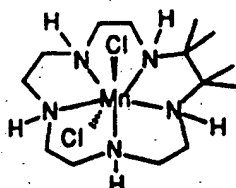
Example 35



SC-55335

 $2.40 \times 10^{7^*}$ 

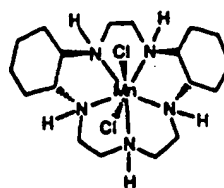
Example 36



SC-55336

 $2.20 \times 10^7$ 

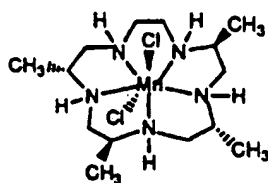
Example 37



SC-55855

 $0.54 \times 10^7$

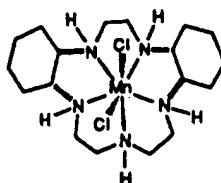
Example 38



SC-55856

 $5.37 \times 10^7$ 

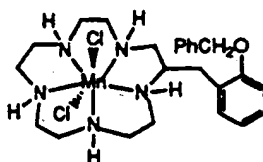
Example 39



SC-55858

 $12.08 \times 10^7$ 

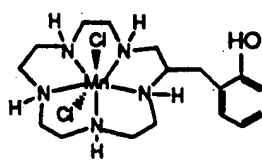
Example 40



SC-55859

 $1.34 \times 10^{7*}$ 

Example 41

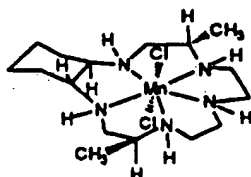


SC-55860

 $6.99 \times 10^7$ 

5

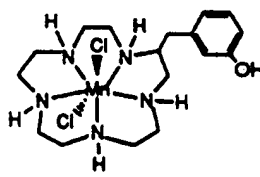
Example 42



SC-56094

 $10.70 \times 10^7$ 

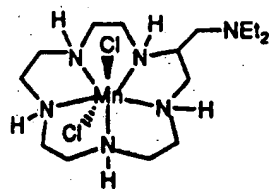
Example 43



SC-56095

 $1.88 \times 10^{7*}$ 

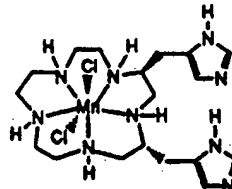
Example 44



SC-56096

 $5.87 \times 10^7$ 

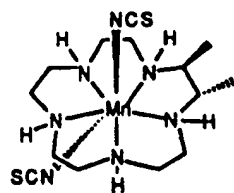
Example 45



SC-56207

 $2.00 \times 10^7$

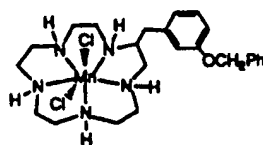
Example 46



SC-56206A

NT

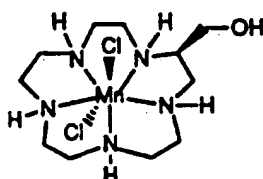
Example 47



SC-56221

 $1.91 \times 10^7$ 

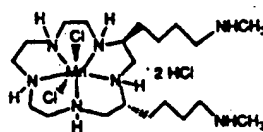
Example 48



SC-56341

 $4.59 \times 10^7$ 

Example 49

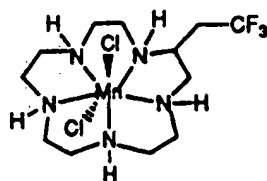


SC-56342

 $5.95 \times 10^7$ 

5

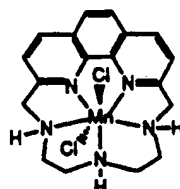
Example 50



SC-56343

 $2.77 \times 10^7$ 

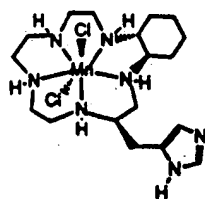
Example 51



SC-56344

NT

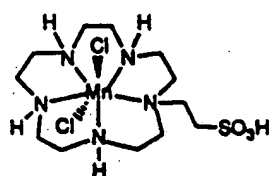
Example 52



SC-56534

 $2.95 \times 10^7$ 

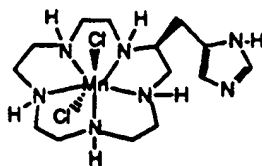
Example 53



SC-56535

NT

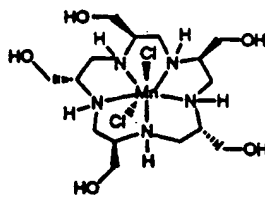
Example 54



SC-56536

 $0.047 \times 10^7$ 

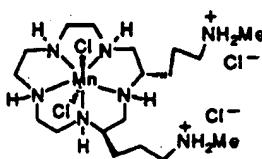
Example 55



SC-56842

 $2.68 \times 10^7$ 

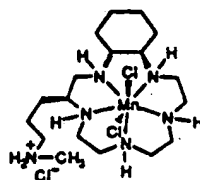
Example 56



SC-56843

 $8.71 \times 10^7$ 

Example 57

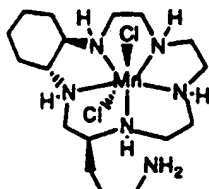


SC-57042

 $5.33 \times 10^7$ 

5

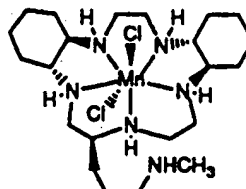
Example 58



SC-57043

 $4.79 \times 10^7$ 

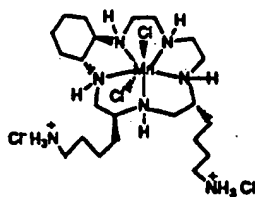
Example 59



SC-57167

 $8.05 \times 10^7$ 

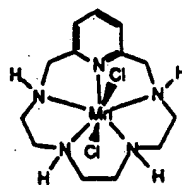
Example 60



SC-57168

 $10.20 \times 10^7$ 

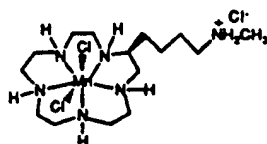
Example 61



SC-57262

 $3.65 \times 10^7$

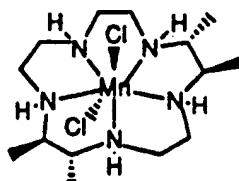
Example 62



SC-57304

 $2.87 \times 10^7$ 

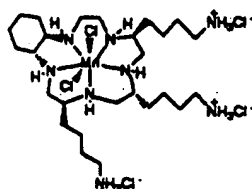
Example 63



SC-57819

 $3.37 \times 10^7$ 

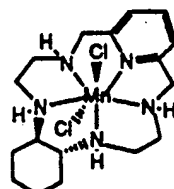
Example 64



SC-57820

 $6.25 \times 10^7$ 

Example 65

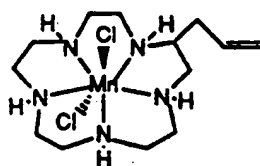


SC-57821

 $1.22 \times 10^7$ 

5

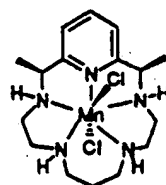
Example 66



SC-57822

 $1.63 \times 10^7$ 

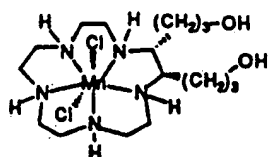
Example 67



SC-58328

 $0.64 \times 10^7$ 

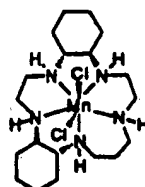
Example 68



SC-58329

 $5.05 \times 10^7$ 

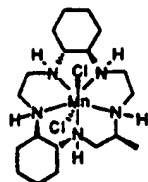
Example 69



SC-58330

 $0.056 \times 10^7$

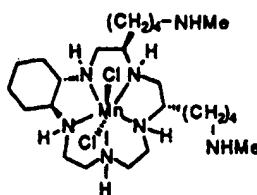
Example 70



SC-58331

 $6.13 \times 10^7$ 

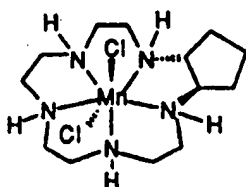
Example 71



SC-58332

 $7.51 \times 10^7$ 

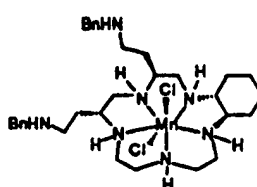
Example 72



SC-58755

 $1.37 \times 10^7$ 

Example 73

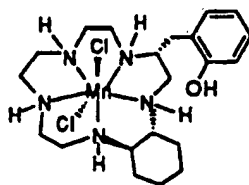


SC-59134

 $1.09 \times 10^7$ 

5

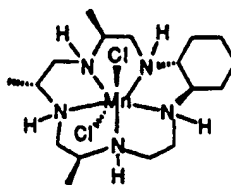
Example 74



SC-59135

 $6.92 \times 10^7$ 

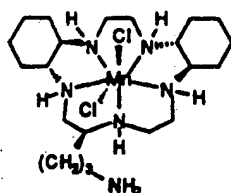
Example 75



SC-59136

 $3.62 \times 10^7$ 

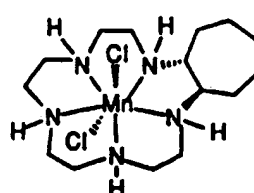
Example 76



SC-59137

 $7.58 \times 10^7$ 

Example 77

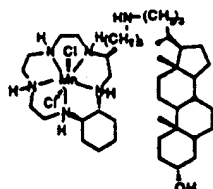


SC-59320

 $5.05 \times 10^7$



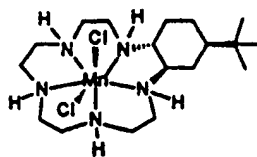
Example 78



SC-59493

 $2.41 \times 10^7$ 

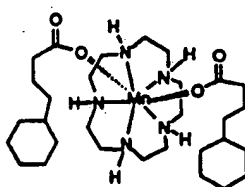
Example 79



SC-59537

 $7.23 \times 10^7$ 

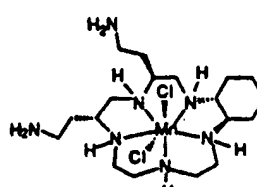
Example 80



SC-59617

 $1.74 \times 10^{10}$ 

Example 81

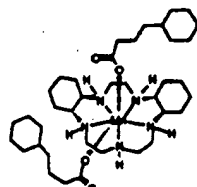


SC-59737

 $2.48 \times 10^7$ 

5

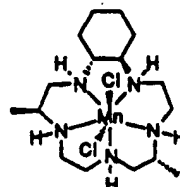
Example 82



SC-60446

NT

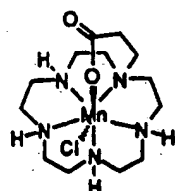
Example 83



SC-60817

 $9.09 \times 10^7$ 

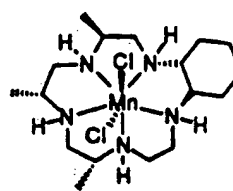
Example 84



SC-60955

0.00

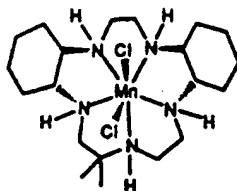
Example 85



SC-63309

 $9.56 \times 10^7$

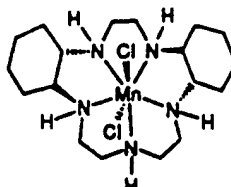
Example 86



SC-63310

 $0.3 \times 10^7$ 

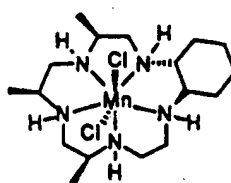
Example 87



SC-63784

 $12.60 \times 10^7$ 

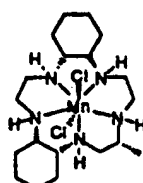
Example 88



SC-64137

 $10.84 \times 10^7$ 

Example 89

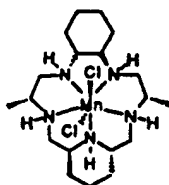


SC-65224

 $15 \times 10^7$ 

5

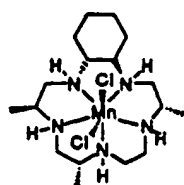
Example 90



SC-65225

 $2.96 \times 10^7$ 

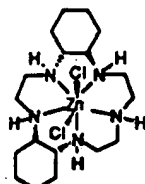
Example 91



SC-65501

 $8.48 \times 10^7$ 

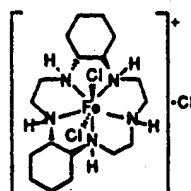
Example 92



SC-65512

NT

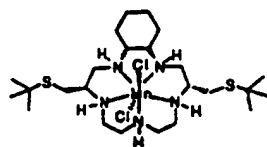
Example 93



SC-65513

 $3.29 \times 10^7$

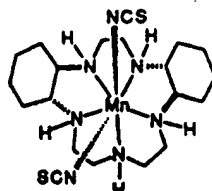
Example 94



SC-65656

 $2.93 \times 10^7$ 

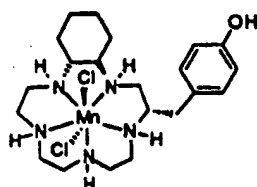
Example 95



SC-66383

 $11.40 \times 10^7$ 

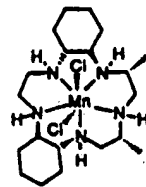
Example 96



SC-67034

 $2.00 \times 10^7$ 

Example 97

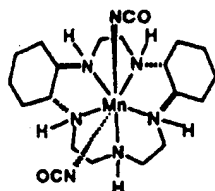


SC-67066

 $3.56 \times 10^7$ 

5

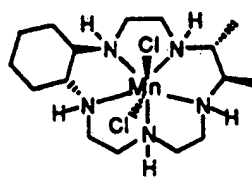
Example 98



SC-67067

NT

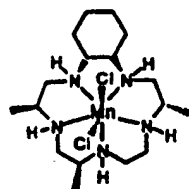
Example 99



SC-67241

 $3.10 \times 10^7$ 

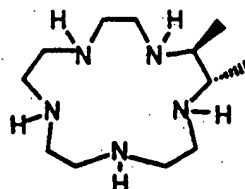
Example 100



SC-67243

 $7.62 \times 10^7$ 

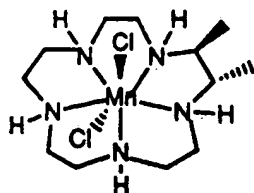
Example 101



SC-68228

NT

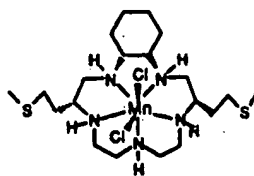
Example 102



SC-68328

 $8.84 \times 10^7$ 

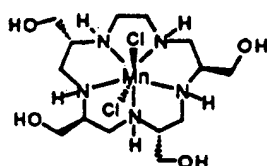
Example 103



SC-68595

 $0.356 \times 10^7$ 

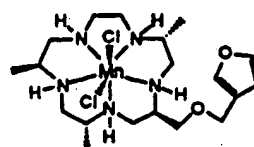
Example 104



SC-69023

 $6.61 \times 10^7$ 

Example 105

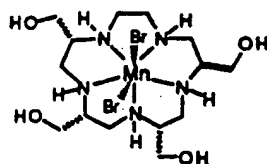


SC-69024

 $2.55 \times 10^7$ 

5

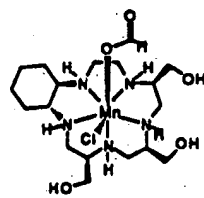
Example 106



SC-69025

 $0.50 \times 10^7$ 

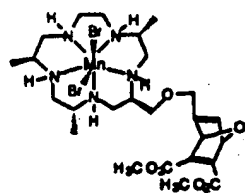
Example 107



SC-69029

0.00

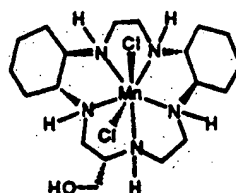
Example 108



SC-69495

 $4.04 \times 10^7$ 

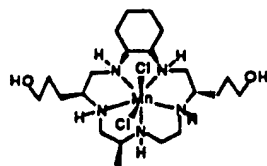
Example 109



SC-69604

 $10.12 \times 10^7$

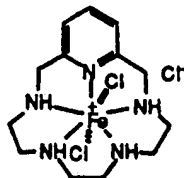
Example 110



SC-69838

 $4.83 \times 10^7$ 

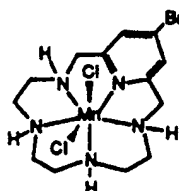
Example 111



SC-70247

NT

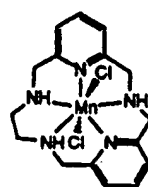
Example 112



SC-70248

 $2.86 \times 10^7$ 

Example 113

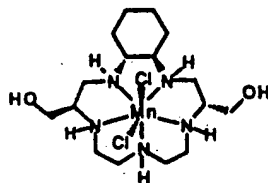


SC-70249

 $0.20 \times 10^7$ 

5

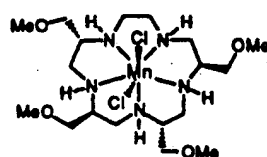
Example 114



SC-70251

 $3.69 \times 10^7$ 

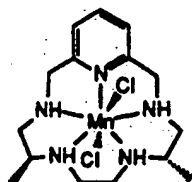
Example 115



SC-70264

 $3.24 \times 10^7$ 

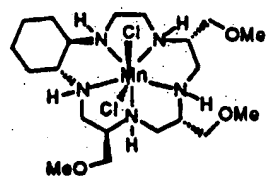
Example 116



SC-70314

 $2.48 \times 10^7$ 

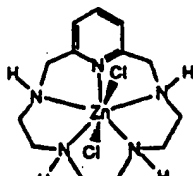
Example 117



SC-70437

 $3.90 \times 10^7$

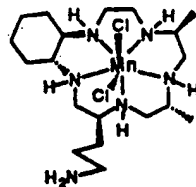
Example 118



SC-70651

NT

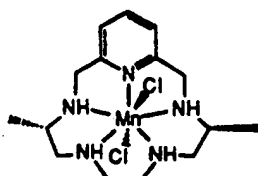
Example 119



SC-70670

 $2.97 \times 10^7$ 

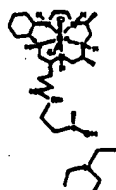
Example 120



SC-70774

 $2.15 \times 10^{10}$ 

Example 121

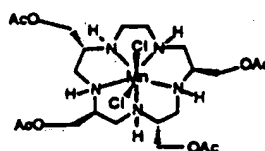


SC-70839

 $1.74 \times 10^{10}$ 

5

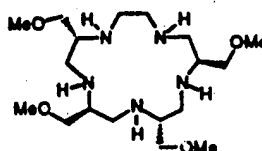
Example 122



SC-71025

 $7.27 \times 10^7$ 

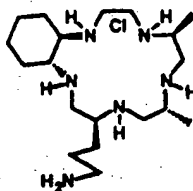
Example 123



SC-71027

NT

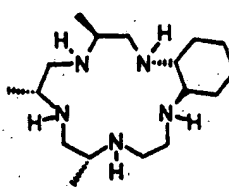
Example 124



SC-71047

NT

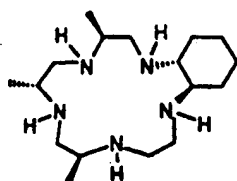
Example 125



SC-71049

NT

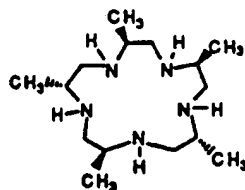
Example 126



SC-71050

NT

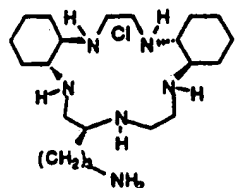
Example 127



SC-71051

NT

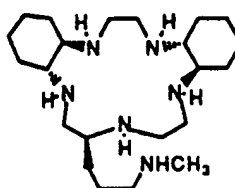
Example 128



SC-71052

NT

Example 129

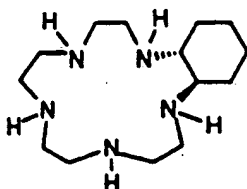


SC-71053

NT

5

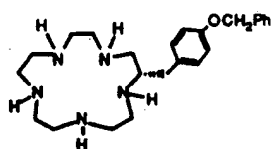
Example 130



SC-71054

NT

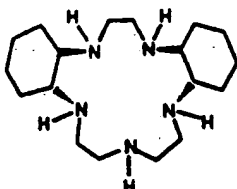
Example 131



SC-71060

NT

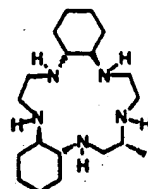
Example 132



SC-71061

NT

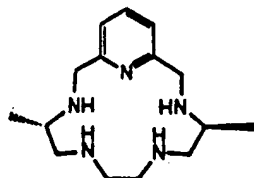
Example 133



SC-71062

NT

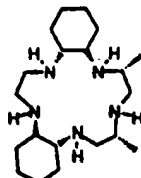
Example 134



SC-71063

NT

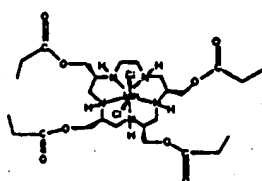
Example 135



SC-71099

NT

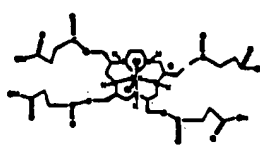
Example 136



SC-71119

$2.70 \times 10^7$

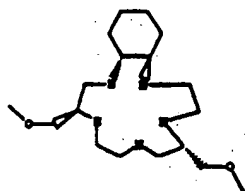
Example 137



SC-71160

0.00

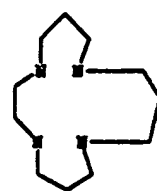
Example 138



SC-71182

NT

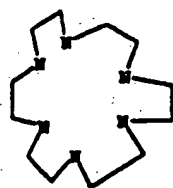
Example 139



SC-71183

NT

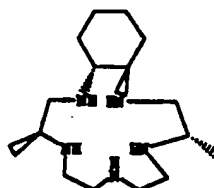
Example 140



SC-71184

NT

Example 141

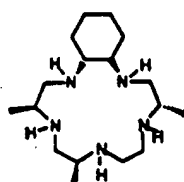


SC-71191

NT



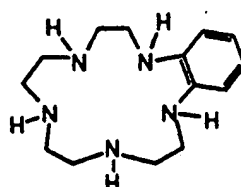
Example 142



SC-71192

NT

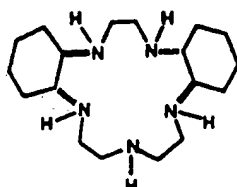
Example 143



SC-71193

NT

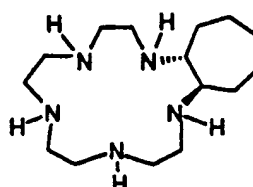
Example 144



SC-71295

NT

Example 145

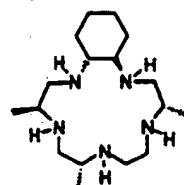


SC-71297

NT

5

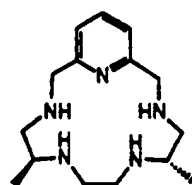
Example 146



SC-71299

NT

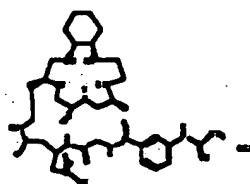
Example 147



SC-71300

NT

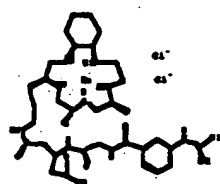
Example 148



SC-71316

NT

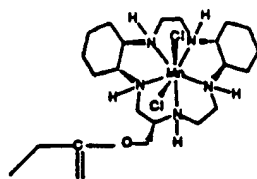
Example 149



SC-71319

4.38 x 10<sup>7</sup>

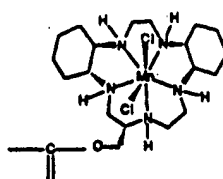
Example 150



SC-71354

 $4.31 \times 10^7$ 

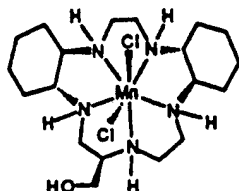
Example 151



SC-71380

 $4.76 \times 10^7$ 

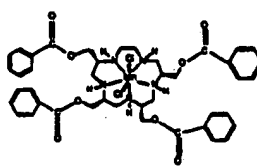
Example 152



SC-71449

 $11.10 \times 10^7$ 

Example 153

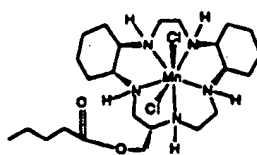


SC-71823

 $0.63 \times 10^7$ 

5

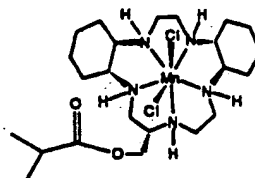
Example 154



SC-71988

 $3.36 \times 10^7$ 

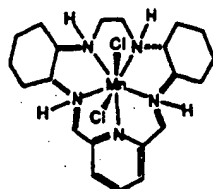
Example 155



SC-72027

 $3.08 \times 10^7$ 

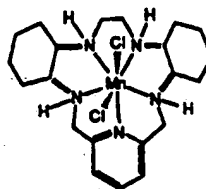
Example 156



SC-72298

0.00

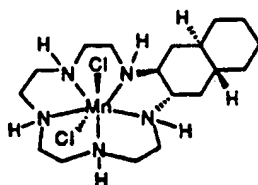
Example 157



SC-72325

 $1.64 \times 10^7$

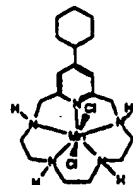
Example 158



SC-72467

 $5.03 \times 10^7$ 

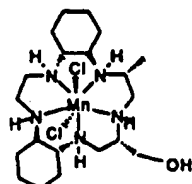
Example 159



SC-72614

 $3.75 \times 10^7$ 

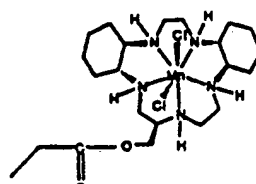
Example 160



SC-72684

 $3.36 \times 10^7$ 

Example 161

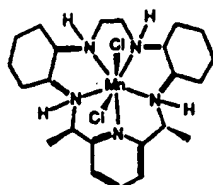


SC-72908

 $3.89 \times 10^7$ 

5

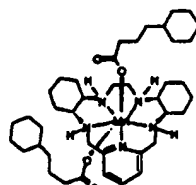
Example 162



SC-73585

0.00

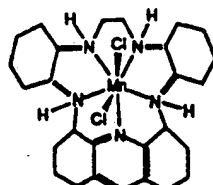
Example 163



SC-73697

NT

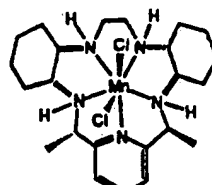
Example 164



SC-73744

 $0.74 \times 10^7$ 

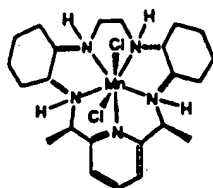
Example 165



SC-73770

 $90.00 \times 10^7$

## Example 166



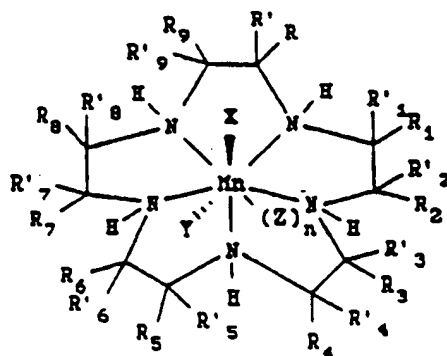
SC-73822

 $1.57 \times 10^7$ 

From the foregoing description, one skilled in the art can easily identify the  
5 essential characteristics of the invention and can make various changes and modifications  
to the invention to adapt it to various usages and conditions without departing from the  
scope and spirit thereof.

1. A method of producing analgesia in a human or lower mammal patient in need of such treatment, comprising administering to the patient an analgesic amount of a functional synthetic catalyst for the dismutation of superoxide radicals.

- 5 2. A method according to Claim 1 wherein the catalyst is a transition metal coordination complex with an organic ligand.
3. A method according to Claim 2 wherein the transition metal is selected from the group consisting of copper, manganese and zinc.
4. A method according to Claim 3 wherein the catalyst is selected from the group
- 10 consisting of compounds of the formula

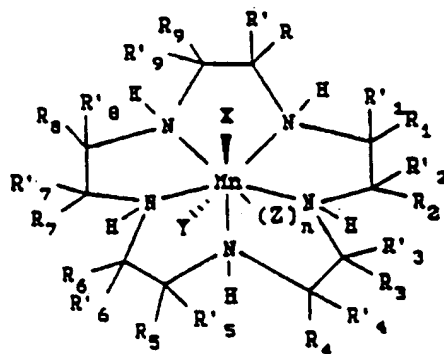


35

- R', R<sub>5</sub> or R'<sub>5</sub>; and R<sub>6</sub> or R'<sub>6</sub>, R<sub>7</sub> or R'<sub>7</sub>, and R<sub>8</sub> or R'<sub>8</sub>, and R<sub>9</sub> or R'<sub>9</sub>, together with the carbon atoms to which they are attached independently form a nitrogen-containing heterocycle having 2 to 20 carbon atoms provided that when the nitrogen containing heterocycle is an aromatic heterocycle that does not have a hydrogen attached to the nitrogen, the hydrogen attached to the nitrogen in the macrocycle and the R groups attached to the same carbon atoms of the macrocycle are absent; R and R', R<sub>1</sub> and R'<sub>1</sub>, R<sub>2</sub> and R'<sub>2</sub>, R<sub>3</sub> and R'<sub>3</sub>, R<sub>4</sub> and R'<sub>4</sub>, R<sub>5</sub> and R'<sub>5</sub>, R<sub>6</sub> and R'<sub>6</sub>, R<sub>7</sub> and R'<sub>7</sub>, R<sub>8</sub> and R'<sub>8</sub> and R<sub>9</sub> and R'<sub>9</sub>, together with the carbon atom to which they are attached independently form a saturated, partially saturated or unsaturated ring structure having 3 to 20 carbon atoms; or two of R, R', R<sub>1</sub>, R'<sub>1</sub>, R<sub>2</sub>, R'<sub>2</sub>, R<sub>3</sub>, R'<sub>3</sub>, R<sub>4</sub>, R'<sub>4</sub>, R<sub>5</sub>, R'<sub>5</sub>, R<sub>6</sub>, R'<sub>6</sub>, R<sub>7</sub>, R'<sub>7</sub>, R<sub>8</sub>, R'<sub>8</sub>, R<sub>9</sub>, and R'<sub>9</sub>, attached to different carbon atoms of the macrocycle are bound to form a strap structure of the formula  

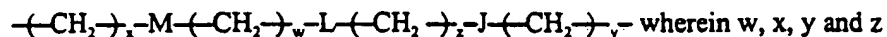
$$-(CH_2)_x-M-(CH_2)_w-L-(CH_2)_z-J-(CH_2)_y-$$
 wherein w, x, y and z independently are integers from 0 to 10 and M, L and J are independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, alkaryl, alkheteroaryl, aza, amido, ammonium, thio, sulfonyl, sulfinyl, sulfonamido, phosphonyl, phosphinyl, phosphino, phosphonium, keto, ester, carbamyl, ureido, thiocarbonyl, borate, borane, boraza, silyl, siloxy and silaza radicals, and combinations thereof; wherein X, Y and Z are pharmaceutically acceptable counterions or together are a pharmaceutically acceptable polydentate ligand, or are independently attached to one or more of the R groups and n is an integer from 0 to 3.
5. A method of preventing or reversing tolerance to opioids in a human or lower mammal patient in need of such treatment, comprising administering to the patient an amount of a functional synthetic catalyst for the dismutation of superoxide radicals sufficient to prevent or reverse such tolerance.
  6. A method according to Claim 5 wherein the catalyst is a transition metal coordination complex with an organic ligand.
  7. A method according to Claim 6 wherein the transition metal is selected from the group consisting of copper, manganese and zinc.

8. A method according to Claim 7 wherein the catalyst is selected from the group consisting of compounds of the formula



wherein R, R', R<sub>1</sub>, R'<sub>1</sub>, R<sub>2</sub>, R'<sub>2</sub>, R<sub>3</sub>, R'<sub>3</sub>, R<sub>4</sub>, R'<sub>4</sub>, R<sub>5</sub>, R'<sub>5</sub>, R<sub>6</sub>, R'<sub>6</sub>, R<sub>7</sub>, R'<sub>7</sub>, R<sub>8</sub>, R'<sub>8</sub>, R<sub>9</sub> and R', independently are selected from the group consisting of hydrogen and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylcycloalkyl, alkylcycloalkyl, cycloalkenylalkyl, alkenylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkenyl, heterocyclic, aryl and aralkyl radicals, or R or R' and R<sub>1</sub> or R'<sub>1</sub>, R<sub>2</sub> or R'<sub>2</sub> and R<sub>3</sub> or R'<sub>3</sub>, R<sub>4</sub> or R'<sub>4</sub> and R<sub>5</sub> or R'<sub>5</sub>, R<sub>6</sub> or R'<sub>6</sub> and R<sub>7</sub> or R'<sub>7</sub>, and R<sub>8</sub> or R'<sub>8</sub> and R<sub>9</sub> or R'<sub>9</sub>, together with the carbon atoms to which they are attached independently form a saturated, partially saturated or unsaturated cyclic ring structure having 3 to 20 carbon atoms; or R or R', R<sub>1</sub> or R'<sub>1</sub>, and R<sub>2</sub> or R'<sub>2</sub>, R<sub>3</sub> or R'<sub>3</sub> and R<sub>4</sub> or R'<sub>4</sub>, R<sub>5</sub> or R'<sub>5</sub> and R<sub>6</sub> or R'<sub>6</sub>, R<sub>7</sub> or R'<sub>7</sub>, and R<sub>8</sub> or R'<sub>8</sub>, and R<sub>9</sub> or R'<sub>9</sub>, together with the carbon atoms to which they are attached independently form a nitrogen-containing heterocycle having 2 to 20 carbon atoms provided that when the nitrogen containing heterocycle is an aromatic heterocycle that does not have a hydrogen attached to the nitrogen, the hydrogen attached to the nitrogen in the macrocycle and the R groups attached to the same carbon atoms of the macrocycle are absent; R and R', R<sub>1</sub> and R'<sub>1</sub>, R<sub>2</sub> and R'<sub>2</sub>, R<sub>3</sub> and R'<sub>3</sub>, R<sub>4</sub> and R'<sub>4</sub>, R<sub>5</sub> and R'<sub>5</sub>, R<sub>6</sub> and R'<sub>6</sub>, R<sub>7</sub> and R'<sub>7</sub>, R<sub>8</sub> and R'<sub>8</sub> and R<sub>9</sub> and R'<sub>9</sub>, together with the carbon atom to which they are attached independently form a saturated, partially saturated or unsaturated ring structure having 3 to 20 carbon atoms; or two of R, R', R<sub>1</sub>, R'<sub>1</sub>, R<sub>2</sub>, R'<sub>2</sub>, R<sub>3</sub>, R'<sub>3</sub>, R<sub>4</sub>, R'<sub>4</sub>, R<sub>5</sub>, R'<sub>5</sub>, R<sub>6</sub>, R'<sub>6</sub>, R<sub>7</sub>,

$R'_7, R_8, R'_8, R_9$ , and  $R'_9$ , attached to different carbon atoms of the macrocycle are bound to form a strap structure of the formula



wherein  $w, x, y$  and  $z$

independently are integers from 0 to 10 and  $M, L$  and  $J$  are independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, alkaryl, alkheteroaryl, aza, amido, ammonium, thio, sulfonyl, sulfinyl, sulfonamido, phosphonyl, phosphinyl, phosphino, phosphonium, keto, ester, carbamyl, ureido, thiocarbonyl, borate, borane, boraza, silyl, siloxy and silaza radicals, and combinations thereof; wherein  $X, Y$  and  $Z$  are pharmaceutically acceptable

counterions or together are a pharmaceutically acceptable polydentate ligand, or are independently attached to one or more of the  $R$  groups and  $n$  is an integer from 0 to 3.

9. An analgesic composition comprising safe and effective amounts of an opioid analgesic compound and a superoxide dismutase catalyst.

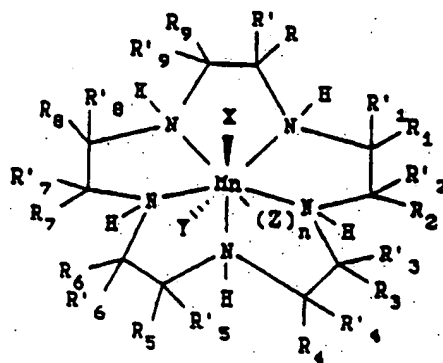
10. A composition according to claim 9 wherein the opioid is morphine.

11. An analgesic composition comprising safe and effective amounts of a nonsteroidal anti-inflammatory compound and a superoxide dismutase catalyst.

12. A composition according to Claim 11 wherein the nonsteroidal anti-inflammatory compound is a cyclooxygenase inhibitor compound.

13. A compound of the formula  $A_n-Q_m$ , wherein  $A$  is a superoxide dismutase catalyst moiety,  $Q$  is selected from nonsteroidal anti-inflammatory drug moieties and opioid analgesic drug moieties, and  $n$  and  $m$  are independently integers from 1 to 3.

14. A compound according to Claim 13 wherein  $A$  is a moiety of the formula





wherein R, R', R<sub>1</sub>, R'<sub>1</sub>, R<sub>2</sub>, R'<sub>2</sub>, R<sub>3</sub>, R'<sub>3</sub>, R<sub>4</sub>, R'<sub>4</sub>, R<sub>5</sub>, R'<sub>5</sub>, R<sub>6</sub>, R'<sub>6</sub>, R<sub>7</sub>, R'<sub>7</sub>, R<sub>8</sub>, R'<sub>8</sub>, R<sub>9</sub> and R'<sub>9</sub>, independently are selected from the group consisting of hydrogen and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylcycloalkyl, alkylcycloalkyl, cycloalkenylalkyl, alkenylcycloalkyl, alkylcycloalkenyl, alkenylcycloalkenyl, heterocyclic, aryl and aralkyl radicals, or R or R' and R<sub>1</sub> or R'<sub>1</sub>, R<sub>2</sub> or R'<sub>2</sub> and R<sub>3</sub> or R'<sub>3</sub>, R<sub>4</sub> or R'<sub>4</sub> and R<sub>5</sub> or R'<sub>5</sub>, R<sub>6</sub> or R'<sub>6</sub> and R<sub>7</sub> or R'<sub>7</sub>, and R<sub>8</sub> or R'<sub>8</sub> and R<sub>9</sub> or R'<sub>9</sub>, together with the carbon atoms to which they are attached independently form a saturated, partially saturated or unsaturated cyclic ring structure having 3 to 20 carbon atoms; or R or R', R<sub>1</sub> or R'<sub>1</sub>, and R<sub>2</sub> or R'<sub>2</sub>, R<sub>3</sub> or R'<sub>3</sub>, and R<sub>4</sub> or R'<sub>4</sub>, R<sub>5</sub> or R'<sub>5</sub>, and R<sub>6</sub> or R'<sub>6</sub>, R<sub>7</sub> or R'<sub>7</sub>, and R<sub>8</sub> or R'<sub>8</sub>, and R<sub>9</sub> or R'<sub>9</sub>, together with the carbon atoms to which they are attached independently form a nitrogen-containing heterocycle having 2 to 20 carbon atoms provided that when the nitrogen containing heterocycle is an aromatic heterocycle that does not have a hydrogen attached to the nitrogen, the hydrogen attached to the nitrogen in the macrocycle and the R groups attached to the same carbon atoms of the macrocycle are absent; R and R', R<sub>1</sub> and R'<sub>1</sub>, R<sub>2</sub> and R'<sub>2</sub>, R<sub>3</sub> and R'<sub>3</sub>, R<sub>4</sub> and R'<sub>4</sub>, R<sub>5</sub> and R'<sub>5</sub>, R<sub>6</sub> and R'<sub>6</sub>, R<sub>7</sub> and R'<sub>7</sub>, R<sub>8</sub> and R'<sub>8</sub>, and R<sub>9</sub> and R'<sub>9</sub>, together with the carbon atom to which they are attached independently form a saturated, partially saturated or unsaturated ring structure having 3 to 20 carbon atoms; or two of R, R', R<sub>1</sub>, R'<sub>1</sub>, R<sub>2</sub>, R'<sub>2</sub>, R<sub>3</sub>, R'<sub>3</sub>, R<sub>4</sub>, R'<sub>4</sub>, R<sub>5</sub>, R'<sub>5</sub>, R<sub>6</sub>, R'<sub>6</sub>, R<sub>7</sub>, R'<sub>7</sub>, R<sub>8</sub>, R'<sub>8</sub>, R<sub>9</sub>, and R'<sub>9</sub>, attached to different carbon atoms of the macrocycle are bound to form a strap structure of the formula

$$-(CH_2)_x-M-(CH_2)_w-L-(CH_2)_z-J-(CH_2)_y-$$

wherein w, x, y and z independently are integers from 0 to 10 and M, L and J are independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, alkaryl, alkheteroaryl, aza, amido, ammonium, thio, sulfonyl, sulfinyl, sulfonamido, phosphonyl, phosphinyl, phosphino, phosphonium, keto, ester, carbamyl, ureido, thiocarbonyl, borate, borane, boraza, silyl, siloxy and silaza radicals, and combinations thereof; wherein X, Y and Z are pharmaceutically acceptable

counterions or together are a pharmaceutically acceptable polydentate ligand, or are independently attached to one or more of the R groups and n is an integer from 0 to 3.

15. A method for treating symptoms of addiction withdrawal in a human or lower mammal patient in need of such treatment, comprising administering to the patient an amount of a functional synthetic catalyst for the dismutation of superoxide radicals  
5 sufficient to reduce such symptoms.

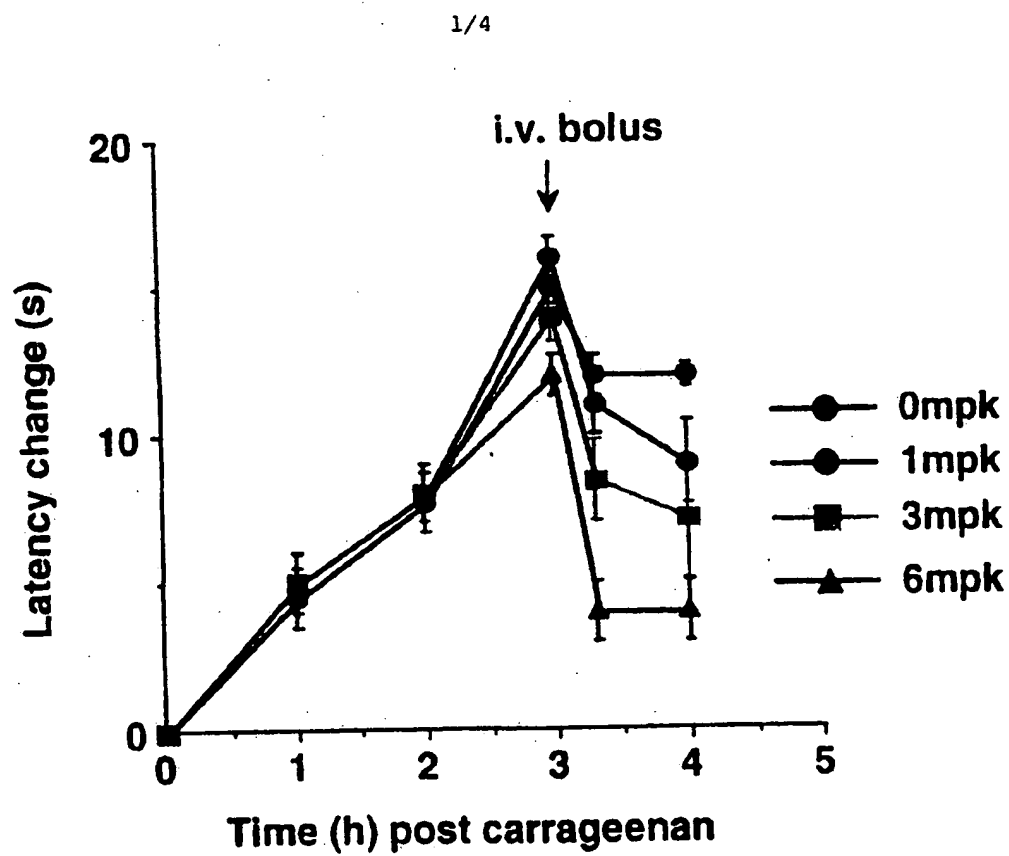


Figure 1

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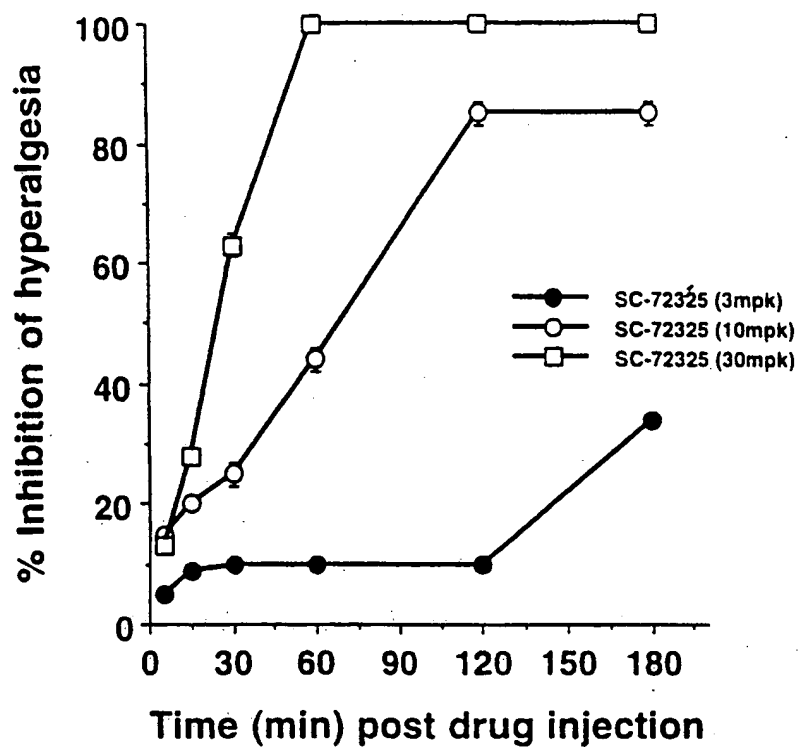


Figure 2

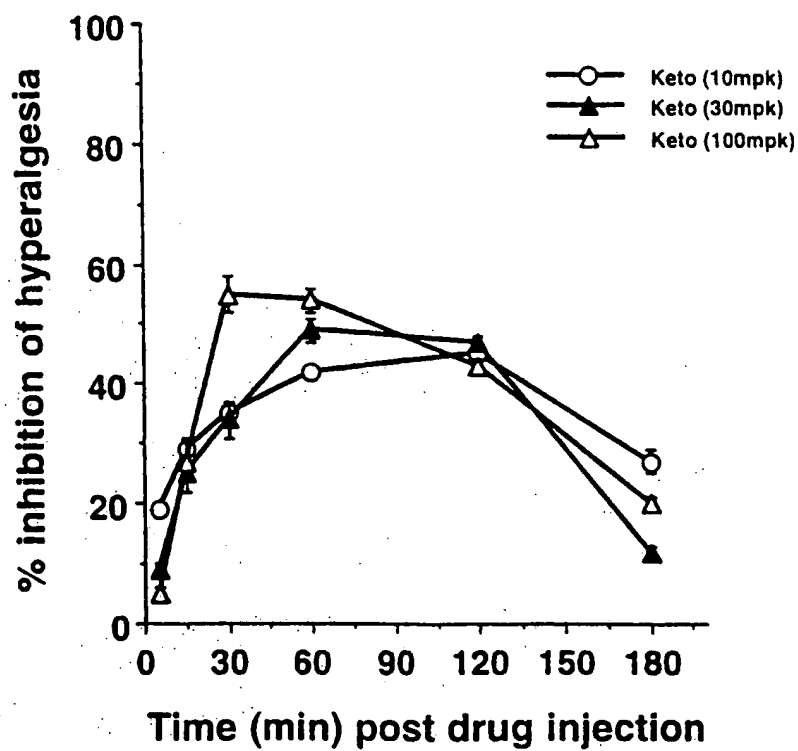


Figure 3

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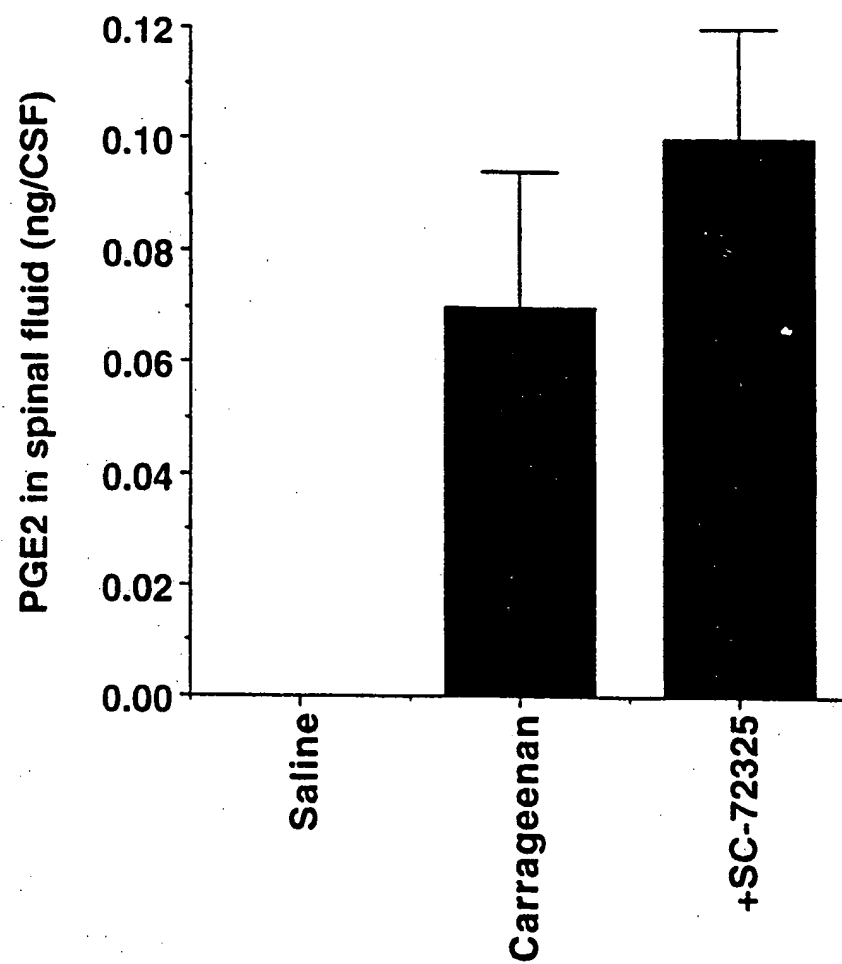


Figure 4

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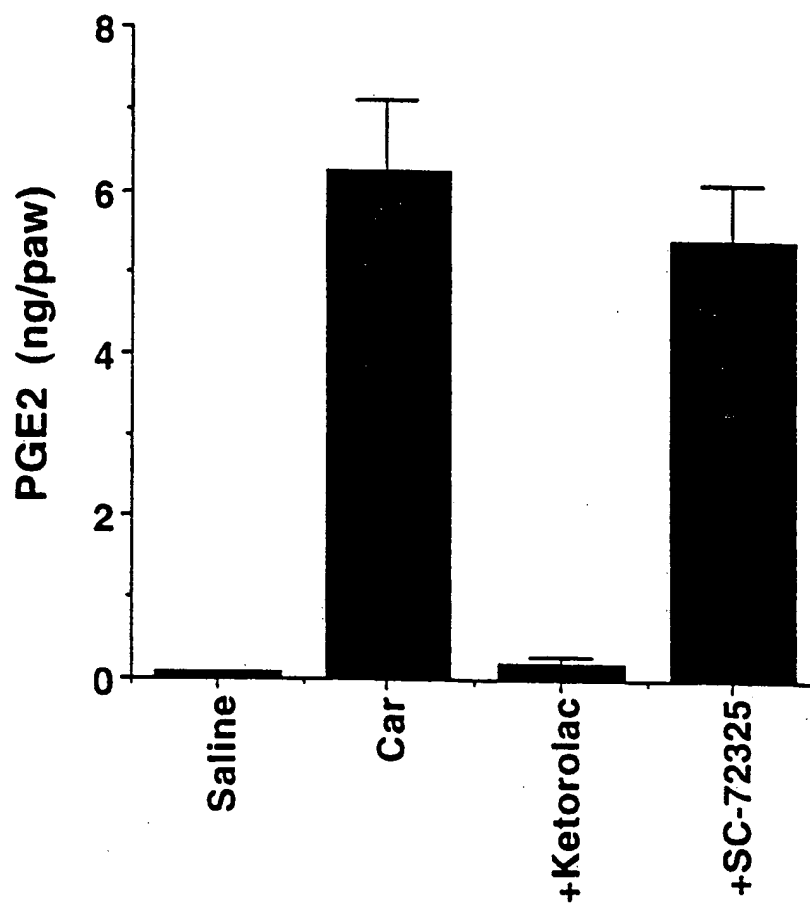


Figure 5

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/12231

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/00 A61K31/555

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	S. OKUYAMA ET AL.: "COPPER COMPLEXES OF NON-STEROIDAL ANTIINFLAMMATORY AGENTS: ANALGESIC ACTIVITY AND POSSIBLE OPIOID RECEPTOR ACTIVATION" AGENTS AND ACTIONS, vol. 21, no. 1/2, 1987, pages 130-144, XP002081028 see the whole document	1-3, 5-7, 9-12
X	US 5 541 174 A (SORENSEN JOHN R J) 30 July 1996 see the whole document	1-3, 5-7, 9-12
X	US 4 999 347 A (SORENSEN JOHN R J) 12 March 1991 see the whole document	1-3, 5-7, 9-12
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

16 October 1998

Date of mailing of the international search report

27/10/1998

Name and mailing address of the ISA

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Authorized officer

Hoff, P

# INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/US 98/12231

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	E. LENGFELDER ET AL.: "SUPEROXIDE DISMUTATION BY LOW MOLECULAR WEIGHT CU-COMPLEXES" CLINICAL RESPIRATORY PHYSIOLOGY, vol. 17, 1981, pages 73-80, XP002081029 see abstract see page 77, paragraph 2; table V	1-3,5-7, 9-12
X	S.T. SHUFF ET AL.: "STABLE SUPEROXIDE DISMUTASE (SOD)-MIMETIC TERNARY HUMAN SERUM ALBUMIN-CU(II)(3,5-DIISOPROPYLSALICYLATE)2 /CU(II)2(3,5-DIISOPROPYLSALICYLATE)4 COMPLEXES IN TISSUE DISTRIBUTION OF THE BINARY COMPLEX" BIOCHEMICAL PHARMACOLOGY, vol. 43, no. 7, 1992, pages 1601-1612, XP002081030 see the whole document	1-3
X	M. TAL: "A NOVEL ANTIOXIDANT ALLEVIATES HEAT HYPERALGESIA IN RATS WITH AN EXPERIMENTAL PAINFUL PERIPHERAL NEUROPATHY" NEUROREPORT, vol. 7, no. 8, 1996, pages 1382-1384, XP002081031 see the whole document	1
X	DATABASE WPI Section Ch, Week 9531 Derwent Publications Ltd., London, GB; Class B04, AN 95-232188 XP002081041 & CN 1 088 086 A (UNIV XIBEI) , 22 June 1994 see abstract	1
X	RT LI ET AL.: "SYNTHESIS AND PHARMACOLOGICAL ACTIVITIES OF 1,1-DIALKYL-4 (3-BROMOPROPIONYL) PIPERAZINIUM BROMIDES" ACTA PHARMACEUTICA SINICA, vol. 31, no. 10, 1996, pages 757-760, XP002081032 see abstract see page 759 see table 3	1

-/-



# INTERNATIONAL SEARCH REPORT

Internatic Application No

PCT/US 98/12231

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	N. GOLDSTEIN ET AL.: "EXOGENOUS GASEOUS SUPEROXIDE POTENTIATES THE ANTINOCICEPTIVE EFFECT OF OPIOID ANALGESIC AGENTS" INFLAMMATION RESEARCH, vol. 45, no. 9, 1996, pages 473-478, XP002081033 see abstract see page 474 see page 476, right-hand column, last paragraph; figure 6 ----	9,10
A	ELMER G I ET AL: "TRANSGENIC SUPEROXIDE DISMUTASE MICE DIFFER IN OPIOID-INDUCED ANALGESIA" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 283, no. 1/03, 1995, pages 227-232, XP000602399 cited in the application see the whole document ----	1-10,15
A	R. VARSANO ET AL.: "SUPEROXIDE DISMUTASE ACTIVITY IN MORPHINE AND MEPERIDINE ADDICTED MICE AND THEIR RESPONSE TO PARAQUAT POISONING" FRESENIUS ENVIR. BULL., vol. 1, 1992, pages S54-S59, XP002081034 see the whole document ----	5-10,15
A	Y.LIN ET AL.: "USE OF SUPEROXIDE DISMUTASE (SOD) IN PATIENTS WITH TEMPOROMANDIBULAR JOINT DYSFUNCTION-A PRELIMINARY STUDY" INTERNATIONAL JOURNAL OF ORAL & MAXILLOFACIAL SURGERY, vol. 23, 1994, pages 428-429, XP002081035 cited in the application see the whole document ----	1-10
X	CHEMICAL ABSTRACTS, vol. 111, no. 15, 9 October 1989 Columbus, Ohio, US; abstract no. 129816, "MODIFIED SUPEROXIDE DISMUTASE AS INFLAMMATION INHIBITOR AND OTHERS" XP002081040 see abstract & JP 63 313581 A (UBE INDUSTRIES) 21 December 1988 ----- -/--	11-13

# INTERNATIONAL SEARCH REPORT

Internatic Application No  
PCT/US 98/12231

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	A. KOHUT ET AL.: "EFFECT OF ALLOPURINOL AND SUPEROXIDE DISMUTASE ON INDOMETHACIN-INDUCED GASTRIC LESIONS IN THE RAT" PHYSIOLOGICAL RESEARCH, vol. 42, 1993, pages 273-276, XP002081036 see the whole document ---	11,12
X	J.L. JOYAVE ET AL.: "ALTERATION OF CHEMICALLY INDUCED HEPATOTOXICITY BY COPPER (II) (3,5-DIISOPROPYLSALICYLATE)2" BIOCHEMICAL PHARMACOLOGY, vol. 34, no. 21, 1985, pages 3915-3919, XP002081037 see abstract see page 3916, left-hand column, last paragraph; tables 5,6 ---	11,12
A	B.C. DEL VILLANO ET AL.: "ELEVATED SUPEROXIDE DISMUTASE IN BLACK ALOHOLICS" SCIENCE, vol. 207, no. 4434, 1980, pages 991-993, XP002081038 see the whole document ---	15
X	EP 0 524 161 A (MONSANTO CO) 20 January 1993 see abstract see page 22, line 10 - line 17; claims; examples ---	1-4
X	WO 96 39396 A (MONSANTO CO ; NEUMANN WILLIAM L (US); RILEY DENNIS P (US); WEISS RA) 12 December 1996 see abstract see page 33, line 30 - page 34, line 7; claims; examples ---	1-4
X	WO 94 15925 A (MONSANTO CO) 21 July 1994 see abstract see page 40, line 30 - page 41, line 9; claims; examples ---	1-4
A	"DORLAND'S ILLUSTRATED MEDICAL DICTIONARY" 1985, W.B.SAUNDERS COMPANY XP002081039 see page 655 "inflammation" -----	1-4

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/ 10918

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 10-13  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/US 98/12231

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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